Vitamin C and the common cold: early systematic reviews and the justification for new trials : [Comment]

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Vitamin C and the common cold: early systematic reviews and the justification for new trials

Vitamin C and the common cold is a particularly important topic in the history of systematic reviews because three of the earliest systematic reviews examined that topic [1-3]. Nevertheless, Bastian et al.'s brief mention of this issue is misleading [4].

There has been a long-lasting belief in the mainstream medicine that vitamin C has effect only on scurvy. Linus Pauling's 1971 systematic review of 4 placebo-controlled studies on vitamin C and the common cold challenged this view [1]. Pauling pooled P-values of the 4 trials by using the Fisher method and calculated that it was highly unlikely that the decrease in common cold morbidity in vitamin C groups was explained by random variation (pooled P = 0.000022). Among the 4 trials included in Pauling's meta-analysis, the greatest benefit was found by Ritzel who studied Swiss schoolchildren in a skiing camp [5]. Ritzel used the highest dose, 1 g/day, and this led Pauling to propose that gram doses of vitamin C might decrease common cold morbidity [1].

Thomas Chalmers' 1975 systematic review [3] challenged the validity of Pauling's conclusions. Chalmers selected 8 placebo-controlled trials and calculated that the common cold episodes were on average 0.11 ± 0.24 (SE) days shorter in the vitamin C groups than in the placebo groups. Even if real, a 0.11 day (= 2.6 hours) decrease in the duration of colds would have no clinical relevance, Furthermore, the great variation in the results indicates that the slight difference is explained by chance. Chalmers concluded that "the conclusion drawn from this analysis of the published controlled trials is the opposite of that drawn from the analysis carried out by Pauling [1], of four trials, published before 1971."

However, Chalmers' systematic review [3] contains a large number of serious errors, such as the data presented was inconsistent with the original published data, there were errors in calculation, the selection of trials was inconsistent, and in some trials a clinically less meaningful outcome was selected. I re-analyzed those trials that were known to Chalmers which had used ≥1 g/day of vitamin C, i.e., which were testing Pauling's proposal. I found that the common cold episodes were 0.93 ± 0.22 (SE) (P = 0.01) days shorter in the vitamin C groups [6,7]. Thus, an estimate of more than 8 times Chalmers' estimate was obtained by employing correct values and keeping to trials which used doses as high as Pauling had proposed. Furthermore, a more useful estimate of vitamin C effect from the same trials is a 21% ± 3% (SE) decrease in common cold duration (P = 0.001) [6].

In our Cochrane review on vitamin C and the common cold [8,9], Ritzel's trial [5] is included in the subgroup of studies with participants under heavy acute physical stress. In this subgroup vitamin C supplementation halved the incidence of colds. Evidently, it was not a misjudgement by Pauling to put the greatest weight on Ritzel's randomized double-blind trial, but when Pauling extrapolated Ritzel's results to all people (i.e., to children at school and to adults), he took a bold step and went wrong [10]. In any case, the data Pauling presented was consistent with the original published data and he did not make errors in calculations.

In their Box 1, Bastian et al. list Chalmers' 1975 systematic review as one of the early systematic reviews, without mentioning that the review was shown to be seriously flawed over a decade ago [6]. At the same time Bastian et al. ignore Pauling's 1971 systematic reviews [1,2] although they were methodologically sound and published 3 years before the first systematic review mentioned in Box 1. Given that the primary purpose of systematic reviews is to minimize the likelihood of being misled by the effects of biases, Bastian et al.'s biased presentation of the early systematic reviews is amazing.

I dont see much justification for Bastian et al.'s proposal that a new controlled trial should not be carried out unless a systematic review has shown the trial to be necessary [4, p. 5]. If researchers had been following Bastian et al.'s way of reasoning, no new vitamin C common cold trials would

have been carried out after Chalmers' 1975 systematic review was published. Although that review largely quelled interest in vitamin C, it is fortunate that some new trials were still carried out. Our Cochrane review shows that even more new trials are needed [8,9]. I have read many poor quality systematic reviews and it would be a pity if all of them had such a great influence that the justification for new trials was based on them. Given that Bastian et al. cannot see that the highly influential Chalmers' 1975 systematic review is seriously flawed, how could less experienced researchers evaluate whether some of the recent systematic reviews is reliable or not when they are contemplating the rationale for a new trial.

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